American Journal of BioMedicine
AJBM 2014;2(4): 133–147
Research Article doi: 10.18081/2333-5106/014-03/ 255-269

Daytime peak incidence of death due to the ischemic heart disease

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Abstract

Myocardial infarction, myocardial ischemia, ventricular dysrhythmias, and sudden cardiac death occur most frequently in the morning, especially in the first few hours after awakening. Among individual patients, however, this pattern may vary widely. Up to 80% of individuals who suffer sudden cardiac death have coronary heart disease; the epidemiology of sudden cardiac death to a great extent parallels that of coronary heart disease. This review describes circadian patterns in cardiovascular disease processes and analyses the findings of recent studies by searched, from PubMed, ISI Web of Science, Google Scholar and Scopus databases in a time period between late 1970s through July 2013. The circadian pattern of numerous cardiovascular events (myocardial infarction, sudden cardiac death, stroke) reveals a peak in the early hours of the morning, which occurs in more than 20% of patients with arterial hypertension, and can be regularly detected in combined 24-h-ABPM/EKG examinations. The awareness of an increased incidence of myocardial infarction and sudden cardiac death in the early morning hours, shortly after waking, has stimulated an interest in the relationship of these events and the occurrence of both silent and symptomatic myocardial ischaemia. A number of studies have been reported that examine both the physiological triggers and the underlying causes of these events. Beta-adrenergic blockers have been shown to abolish the early morning peak of myocardial infarction and blunt the morning peak in sudden cardiac death. Newer calcium antagonists, such as amlodipine, have been demonstrated to control angina throughout a 24-hour period. Aspirin is effective in preventing morning infarction. Approaching the pathophysiology of circadian time-dependent sudden cardiac death has implication for future prevention and treatment.

Key words: Myocardial infarction; Sudden cardiac death; Stroke; Coronary heart disease; Hypertension

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Received May 11, 2014; Accepted September 08, 2014, Published October 03, 2014

Introduction

Myocardial infarction, myocardial ischemia, ventricular dysrhythmias, and sudden cardiac death occur most frequently in the morning, especially in the first few hours after awakening [1]. Among individual patients, however, this pattern may vary widely. Up to 80% of individuals

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who suffer sudden cardiac death have coronary heart disease; the epidemiology of sudden cardiac death to a great extent parallels that of coronary heart disease [2].

This review describes circadian patterns in cardiovascular disease processes and analyses the findings of recent studies by searched, from PubMed, ISI Web of Science, Google Scholar and Scopus databases in a time period between late 1970s through July 2013 [3]. The circadian pattern of numerous cardiovascular events (myocardial infarction, sudden cardiac death, stroke) reveals a peak in the early hours of the morning, which occurs in more than 20% of patients with arterial hypertension, and can be regularly detected in combined 24-h-ABPM/EKG examinations [4].

The awareness of an increased incidence of myocardial infarction and sudden cardiac death in the early morning hours, shortly after waking, has stimulated an interest in the relationship of these events and the occurrence of both silent and symptomatic myocardial ischemia [5]. A number of studies have been reported that examine both the physiological triggers and the underlying causes of these events. Beta-adrenergic blockers have been shown to abolish the early morning peak of myocardial infarction and blunt the morning peak in sudden cardiac death. Newer calcium antagonists, such as amlodipine, have been demonstrated to control angina throughout a 24-hour period. Aspirin is effective in preventing morning infarction. Approaching the pathophysiology of circadian time-dependent sudden cardiac death has implication for future prevention and treatment [6].

Ischemic heart disease (IHD) is the main global cause of death, accounting for >9 million deaths in 2016 according to the World Health Organization (WHO) estimates [7] Mortality from IHD in Western countries has dramatically decreased throughout the last decades with greater focus on primary prevention and improved diagnosis and treatment of IHD. However, developing countries pose new challenges for public health. While globalization often improves health care systems, the adoption of Western lifestyles can lead to higher prevalence of cardiovascular risk factors [8].

Previous studied the global epidemiology of IHD from 1995 to 2012 [9]. In this article, we provide an update, reporting on the burden of IHD mortality up to 2013. Mortality data will be presented by country, sex, and income [10].

We provide additional country-based analyses of mortality rates by sex, mortality rate changes over time, and risk factors. We display how trends of mortality from IHD in these countries have evolved over the last decade, comparing them with mortality from the major noncommunicable diseases (NCDs) described by the WHO alongside liver disease, infectious disease, and transport accidents as points of reference. Governments worldwide are trying to address risk factors of NCDs [11]. Therefore, we also analyze how the prevalence of hypertension, smoking, obesity, and diabetes mellitus has changed during these years.

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Risk Factors

Mortality from NCDs is expected to rise in the coming decades due to worsening of metabolic risk factors. This should result from a worsening of metabolic risk factors, particularly high BMI, diabetes mellitus, hypertension, and high cholesterol. Tobacco consumption is supposed to be decreasing but could easily become the leading risk factor for years of life lost according to the worse health scenarios [12]. Targeting these risk factors through public health policies may be the best way to interrupt this trend.

Risk factor prevention campaigns have been historically popular in high-income countries. Examples of this include increased taxation on cigarettes, health warnings on tobacco products, banning smoking in public areas, blood pressure testing events in big cities, and mass media campaigns promoting healthy behavior [13].

However, the growing adoption of Western lifestyle may contribute to an increasing prevalence of risk factors in developing countries, where there may be less access to such programs [14]. The United Kingdom and United States have a lower prevalence of diabetes mellitus and hypertension than Brazil, Kazakhstan, and Ukraine. Mean BMI is highest in United States (out of the 5 countries analyzed), but there is an upward trend of BMI in Brazil. Tobacco control has always been one of the biggest public health challenges and a lot of advocacy interventions to reduce smoking explain the overall decreasing trend.

A cross-sectional study published in 2012 has stated poor awareness of the need for cardiovascular risk factor control in Kazakhstan [15]. The Global Conference on Primary Health Care, held in Astana in October 2018, reported insufficient primary health care for most developing countries [16].

Uncontrolled high blood pressure has been described as the leading cause of high IHD burden in former Soviet Union countries. Low adherence to antihypertensive treatments in these countries has been reported. This seems to be because of an insufficient health expenditure that forces patients to out-of-pocket payments to access medications [17].

At the same time, IHD mortality is high even in the United Kingdom and risk factors are likely to play a crucial role in explaining its rates. Interestingly, there is variability among different areas of the nation, with a higher association between risk factors and years of life lost in more deprived socioeconomic areas [18].

A poor awareness about cardiovascular risk factors in young US adults has also been observed, and those with barriers to health care, such as lack of insurance, were more likely to be unaware [19].

One way to reduce death from IHD may be to implement public health campaigns focused on primary prevention supported by a primary care infrastructure, extending them both to low- and middle-income countries and to groups with low socioeconomic status in high-income countries. The increasing statin prescription rates in the United Kingdom may indicate an increasing effort of a high-income country to prevent cardiovascular diseases or a rise in prevalence of hypercholesterolemia although this seems less likely [20].

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Standardized rates are preferable for comparing countries because they remove the effects of population size and age structure. The most comprehensive standardisation is direct standardisation (Fig. 1 published previously), which requires age-specific data for both the number of deaths in each country and its population size. In many countries age-specific data on deaths from IHD are not available, but the UN does provide modelled estimates of age-specific population counts for all countries. Indirect standardisation (Fig. 2) divides the deaths observed in a country, by the deaths expected if that country had the same age-specific death rates as a population group chosen to be the standard for comparison. We present indirectly standardised ratios for countries where direct standardisation is not possible due to lack of age-specific death data.

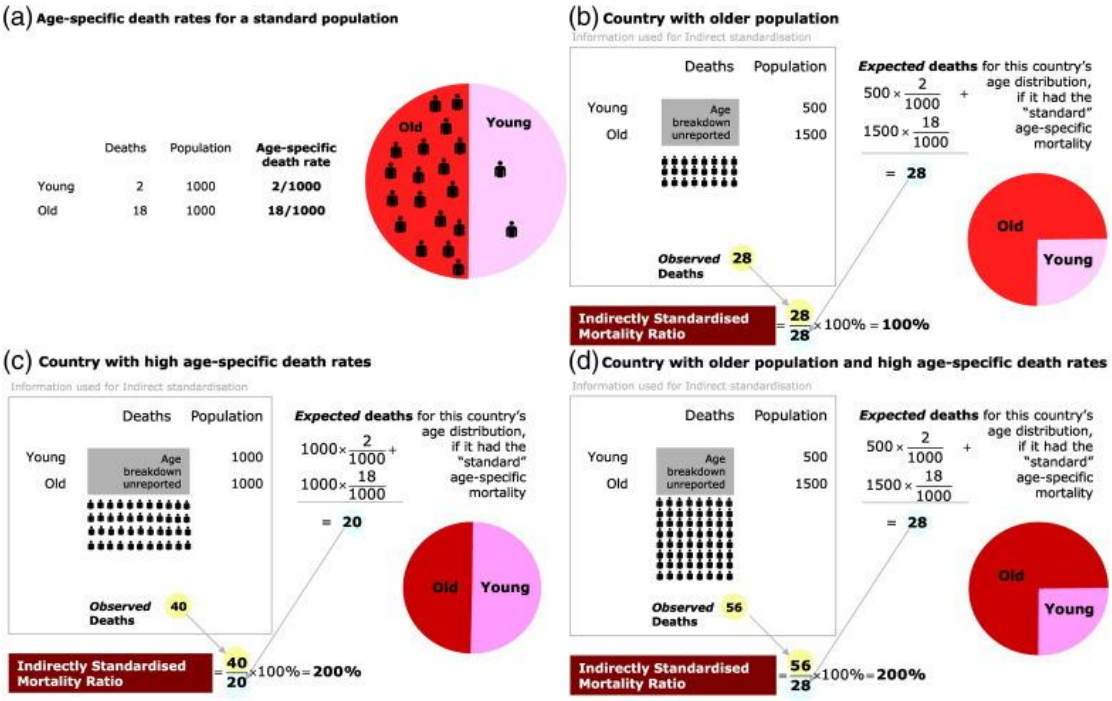

Figure 1.

If a country reports age-specific population but only total IHD deaths (without an age breakdown), it is not possible to calculate directly standardised mortality rates. Instead, by making the assumption that the age relationship of mortality is a scaled-up or scaled-down version of that of a standard population, it is possible to calculate an indirectly standardised mortality ratio expressing the country's mortality relative to that of the standard population. Panels (b), (c) and (d) calculate the indirectly standardised mortality ratio for the same country data as the corresponding panels in Figure 1, but with the age breakdown of deaths concealed.

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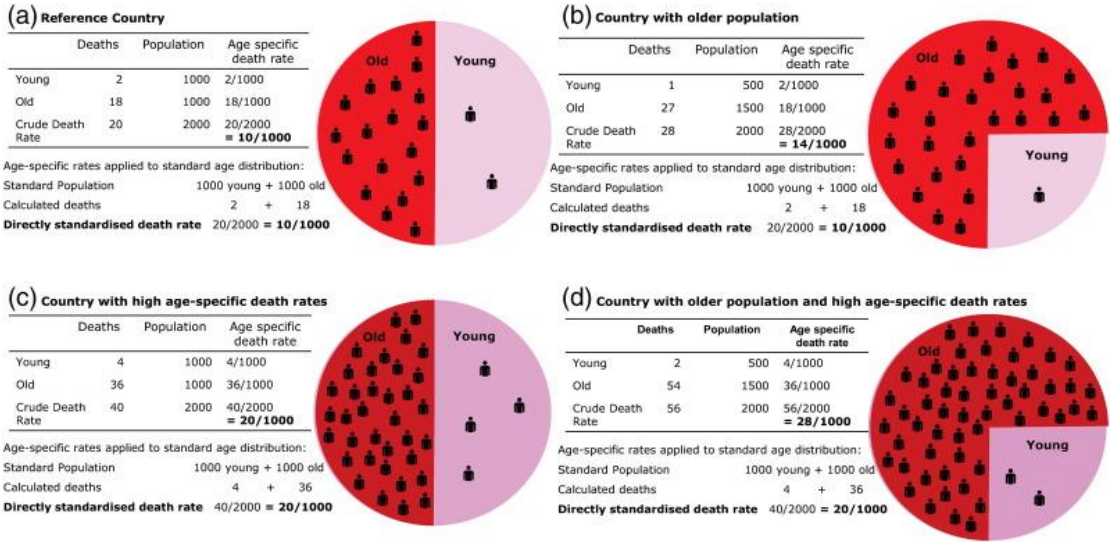

Figure 2.

A standard population of 2000 people, distributed equally amongst "young" (under 60 years) and "old" (60 years and older) groups which have different death rates. This distribution of ages will be used as the "standard" in the other panels. (b) A country with the same age-specific risks, but whose population is older. Crude death rate is higher because a greater proportion of people are in the high-risk age group. However, age-standardisation prevents the ageing artefact by reconstituting a population of the "standard" age distribution, to obtain the same standardised death rate as (a). (c) A country which, compared with (a), has double the death rate at each age group. Crude death rates, and age-standardised death rates are doubled (d) A country with double the age-specific mortality and an older population. Crude mortality is very much higher but age-standardised mortality, which reconstitutes a standard distribution of ages, is only twice that of panel (a).

Burden of IHD worldwide in 2010

The burden of IHD deaths in 2010 in countries for which data were available. Of these 71 countries, Russia, the United States of America and Ukraine account for the largest numbers of deaths. Startlingly, Ukraine had almost as many deaths as the United States of America yet the United States of America's population is over 6 times larger than that of Ukraine [21].

The global distribution of deaths from IHD has been estimated for the majority of countries in 2010. This is illustrated in Fig. 1 in the form of a map where country area has been transformed to provide a visual representation of the numbers of deaths: larger country areas indicate larger numbers of deaths. The five countries with the greatest numbers of estimated deaths are India, China, Russia, the United States of America and Ukraine in descending order. The darker shaded areas indicate higher standardised mortality ratios. The five with the highest rates are Turkmenistan, Ukraine, Belarus, Uzbekistan and Kazakhstan in descending order [22].

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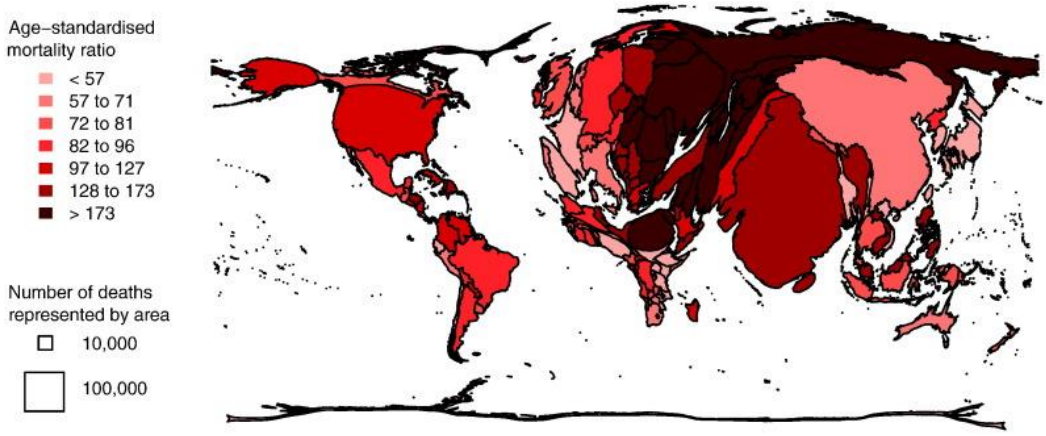

Figure 3.
Cartogram showing the worldwide distribution of IHD mortality using 2010 estimates from the Institute for Health Metrics and Evaluation.

Impact of age on IHD mortality

Fig. 4 a–d (previously published) shows the large increase in mortality in each sex in the 4 countries selected (Ukraine, Russia, the United Kingdom and Japan) because their mortality rates are some of the highest and lowest in the world and recent data was available. In men there was a 2.3- to 2.9-fold increase in IHD mortality per decade and a 3.2- to 4.5-fold increase in women [23].

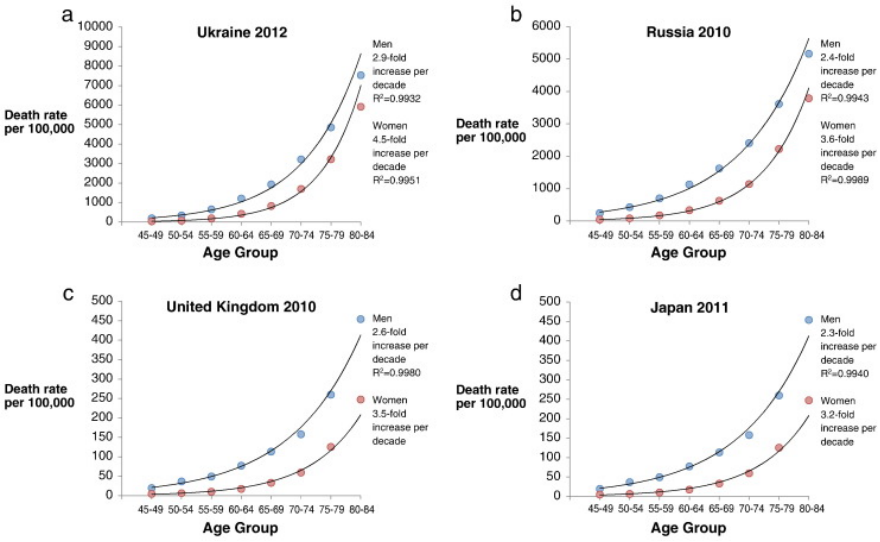

Figure 4.
Variation in mortality with age for (a) Ukraine, (b) Russia, (c) the United Kingdom and (d) Japan.

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Age specific mortality rates from IHD in 2001

Age specific mortality rates for IHD were higher in low-and-middle income countries than in high income countries (Tables 2a and 2b). For older ages highest rates were seen in Europe and Central Asia, South Asia and the Middle East and North Africa. For example, for men in the age range 80 years and over the death rates per 100,000 population were 8598 in Europe and Central Asia, 3758 in Middle East and North Africa and 3644 in South Asia. Meanwhile in high income countries the rate was 2253 per 100,000 population [24].

Table 1.

Age specific death rates from IHD in 2001 male and female.

Regions	Age specific death rates from IHD (per 100,000 population)							
	0–4	5–14	15–29	30–44	45–59	60–69	70–79	80 +
Low income countries								
East Asia and Pacific	1	1	3	15	79	304	779	1606
Europe and Central Asia	0	0	6	89	517	1591	3571	8598
Latin America and Caribbean	0	0	3	17	126	414	939	1956
Middle East and North Africa	0	0	5	45	304	956	2156	3758
South Asia	2	2	5	35	302	1005	2207	3644
Sub-Saharan Africa	0	0	1	14	139	526	1345	2291
High income countries								
High income countries	0	0	1	13	91	298	805	2253

Data from the World Health Organisation.

	Age Specific Death Rates from IHD (per 100,000 population)							
Regions	0–4	5–14	15–29	30–44	45–59	60–69	70–79	80 +
Low income countries								
East Asia and Pacific	0	0	3	8	47	227	647	1776
Europe and Central Asia	0	0	2	16	132	666	2261	7911
Latin America and Caribbean	0	0	1	7	55	223	567	1758
Middle East and North Africa	0	0	2	16	137	587	1565	3618
South Asia	2	1	9	25	163	790	1945	3217
Sub-Saharan Africa	0	0	1	6	86	410	1041	2212
High income countries								
High income countries	0	0	0	3	23	107	401	1789

Data from the World Health Organisation.

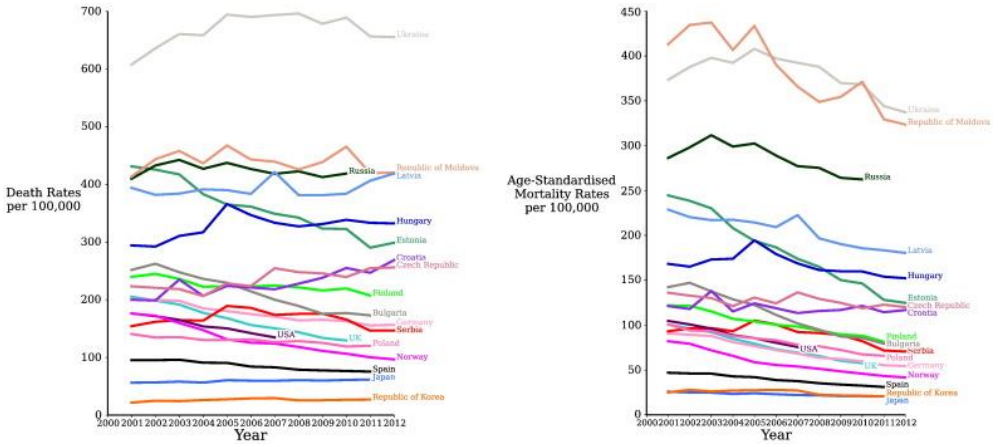

Figure 5.

Changes in (a) crude death rates and (b) directly standardised mortality rates from IHD for selected countries between 2001 and 2012.

Impact of Globalization

We have focused on 5 countries illustrating different steps of globalization. The United Kingdom and United States are a high-income developed country. In both of them, mortality from IHD, as well as from the other chronic treatable diseases, is progressively decreasing [25].

In Brazil, an important epidemiological transition has occurred since the 1960s, leading cardiovascular diseases to become the leading cause of mortality. This happened in parallel with urbanization and economic growth [26]. At present, the profile of mortality from chronic diseases in Brazil is relatively stable, and trends are closer to those observed in United Kingdom rather than in another upper-middle income country, such as Kazakhstan.

In contrast with Brazil, Kazakhstan has more recently undergone globalization. Kazakhstan gained its independence from the Soviet Union in 1991, and since then underwent a rapid growth that led it to become the strongest performing economy in central Asia based on gross domestic product per capita [27].

This may, in part, be related to being an oil exporter. Kazakhstan is also the largest country in Central Asia. The rising prevalence of most cardiovascular risk factors is probably the consequence of its political and economic transition, perhaps through unhealthy lifestyle choices like poor diet and lack of exercise. Another explanation might be that improved healthcare led to increased life expectancy allowing time for cardiovascular risk factors to develop. A similar trend has been noted in China [28].

Kazakhstan was originally a nomad country, and economic development alongside building of modernized towns such as the capital Astana may have promoted the spread of unhealthy lifestyles during the past 2 decades. At the same time, however, increasing wealth is leading to a drastic decrease in age-standardized mortality rates from IHD that have become comparable to those observed in United Kingdom in the last years.

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Ukraine is a low-income country, which was part of the Soviet Union until 1991. From the countries who have provided mortality data to WHO, Ukraine has the highest age-standardized mortality rates from IHD.

The high IHD mortality rate in Ukraine is in line with other former Soviet Union countries, which have not achieved the improvement in mortality rates seen elsewhere. While Ukraine is a noticeable outlier, this may be because other low-income countries such as those in Africa have not provided data to the WHO for comparison in this analysis [29]. Poor risk factor control is likely to be contributing to this, as the results concerning smoking and hypertension prevalence have shown.

Additionally, several other risk factors, such as alcoholism and psychosocial stress, have been described to play a role in cardiovascular mortality in Eastern Europe [4]. Thus, both accurate prevention politics and a consistent income growth, not observed in the last decade, would be necessary to address the IHD epidemic in Ukraine.

Discussion

IHD remains the leading cause of death worldwide. IHD mortality data show that the largest numbers of IHD deaths occurred in Russia, the United States of America and Ukraine (Table 1). However, estimates indicate that India and China, countries for which no recent mortality data is available, have even larger numbers of deaths (Fig. 1).

The marked age dependence of IHD mortality rate is concordant between countries even when the countries have very different mortality rates. Provision of IHD mortality data from most countries is limited for reasons which are not clear.

IHD has been, and continues to be, the single largest cause of death in the world. This is because the majority of the world's population lives in low-and-middle income countries, where IHD mortality rates are often flat or increasing, and total populations are growing.

Overall, age-standardised mortality has fallen significantly in many high income countries since the early 1980s [11]. However, the age effect on IHD mortality is so strong that high income countries, which have older and ageing populations, have a total mortality burden which remains high and is falling only slowly over time.

The larger populations and higher age-specific death rates for IHD in low-and-middle income countries mean that they already account for the majority of global IHD deaths and will bear the brunt of the IHD epidemic in the years to come. Moreover, the combined effect of population growth and ageing is so strong that despite all current efforts, total numbers of IHD deaths worldwide are increasing.

Of the many factors that contribute to the favourable trend in IHD mortality in high income countries, three may be particularly important [11]. Firstly, policy changes may favour risk factor modification, such as decreased exposure to tobacco smoke [17] and improvement in primary prevention strategies [6] (e.g. hypertension control [9]). Second, rapid response times and improved treatments (such as thrombolysis and primary angioplasty) for acute IHD events may

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lead to reduced IHD case-fatality [9]. Third, secondary prevention, which may further reduce mortality, is making more headway in implementation in wealthier countries [17].

The contribution of these factors to the decreasing mortality rates from IHD is complex. The WHO MONICA (MONitoring trends and determinants In CArdiovascular disease) study [29,30] reported that between the mid-1980s and 1990s, on average two thirds of the decline in mortality from IHD could be attributed to a decline in coronary event rates and one third to decreasing case-fatality. A more recent study [9] during the 2000s in England reported just over half of the decline in IHD mortality could be attributed to a decline in event rates and just less than half to improved survival at thirty days.

The increasing mortality in some countries in Eastern Europe is likely to reflect a combination of continued high exposure to cardiovascular risk factors (including tobacco smoke [5]) and inadequate prevention strategies e.g. poor control of hypertension [8]. In addition, evidence suggests a positive association between excess alcohol consumption in Eastern European countries and increased mortality from cardiovascular disease [7]. Unfortunately, data are sparse for many areas of the world e.g. Latin America, Africa that are likely to be incurring continued unfavourable trends in IHD mortality due to rapid urbanisation and the shifting focus of tobacco companies and processed food and drinks manufacturers to low-and-middle income regions [27]. Rapid urbanisation has been positively associated with risk factors related to IHD [28] e.g. smoking, high BMI, poor blood pressure control and lower physical activity. Without accurate baseline mortality data, it will be difficult to target prevention strategies for the future.

Age-standardised mortality from CVD, CHD, and stroke has declined by around 70% over the last 30 years, with even larger declines in premature mortality. Northern Ireland has seen the largest decreases of all UK countries. CVD prevalence appears to have increased slightly in England and Scotland, and data for Great Britain shows the largest increases were in men and women aged over 65. CHD prevalence shows evidence of a small decline over the past decade, while stroke prevalence increased slightly in all UK countries. Hospital admissions for CVD increased over the last decade, although patterns differed for CHD and stroke, with increases seen for some UK countries. The numbers of prescriptions and operations for CVD have increased over the last 20–30 years [6].

The GBD study compared mortality rates in 1990 to those in 2013, and standardised to the GBD 2013 standard population [8]. When standardised to the 2013 ESP, between the same years our data showed greater decreases in CVD, CHD, and stroke mortality than the GBD; however, the use of a different standard population and slightly different methods may explain the differences. These large declines in CVD, CHD, and stroke mortality are consistent with other countries in both Europe and the USA [28].

The BRHS and a GPRD study have both compared CHD prevalence between 2 years to give an estimate of time trends (1979 to 1996 and 1999 to 2007, respectively). The findings from the BRHS are in line with the trends reported here which indicated little evidence of a change

in CHD prevalence over the last decade [23] The GPRD study reported a decrease in absolute numbers of patients living in the community with CHD [24]. These two studies use different data sources, age ranges, and time periods, therefore the discrepancy in their findings may be due to these differences. The GPRD study used a sample of general practice records for those aged over 25, whereas the BRHS asked men from 24 British towns in a longitudinal cohort who were aged 40–59 at recruitment to recall if they have ever had a diagnosis of CHD. The age-specific trends presented in figure 2 indicate an increase in CVD prevalence in only the older age groups over the past 20 years, but it is feasible that this trend is driven more by stroke prevalence than CHD prevalence.

A study using the GPRD to assess changes in stroke incidence and prevalence reported a 12.5% increase in stroke prevalence between 1999 and 2008 [25]. These findings are in line with the trends we report in this review, which found an increase in stroke prevalence between 2003 and 2014 using both QOF data and data from the Health Survey for England and the Scottish Health Survey.

We do not report directly on incidence trends in this review, although FCEs can be used as a proxy for incidence. For England, report a 33% and 31% decline in the incidence of myocardial infarction in men and women, respectively, between 2002 and 2010, using hospital episodes linked to mortality data [23]. Although we report on CHD rather than myocardial infarction, trends in FCEs alone also showed a decrease between 2005/2006 and 2013/2014 for men and women in England. Other study compared trends in hospital admissions for acute myocardial infarction between 1999 and 2007 in England and reported a decrease of around 8000 admissions for both men and women [26]. The decreases we report for CHD demonstrate the same pattern in England, with a decrease in FCEs for CHD over the last decade.

Trends in the incidence of stroke have been reported on using the GPRD and an Oxfordshire based primary care dataset. GPRD data compared 1998 and 2008 and showed a 30% decrease in stroke incidence for the UK during this period [27]. The Oxford Vascular Study reported on stroke incidence in Oxfordshire by comparing rates between 1981 and 1984 with those between 2001 and 2004 [28]. During this 20-year period they report a 29% reduction in stroke incidence (first stroke only), which corroborates the GPRD study findings. The data we present here are for a later time period but also indicate that there was an overall decline in UK stroke admissions.

There were differential trends in stroke admissions between the countries of the UK. England and Wales admissions data are for a longer time period (2005/2006 to 2013/2014), whereas Scotland and Northern Ireland data are from 2009/2010 and 2010/2011, respectively. Using the period between 2010/2011 and 2013/2014 only, stroke admissions in England do show a decline, particularly for women, but a small increase in admissions is still evident for Wales. A 2010 systematic review of stroke incidence in the UK reported that there is limited information on how stroke incidence varies by region of the UK [29], but that from the five studies included in the review, patterns of incidence rates largely mirror patterns of stroke mortality rates around

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the UK [30]. Data in our review demonstrate that stroke mortality rates have decreased. Although 2011 to 2013 only includes 3 years of data, the decrease in stroke mortality between these years was 2% in Wales, compared to 8% in England, 5% in Scotland, and 7% in Northern Ireland, suggesting that a different trend of stroke incidence in Wales may indeed be present for the most recent years.

Despite large decreases in mortality, increases in CVD, CHD, and stroke prevalence were small, with the exception of men over 75 who saw a 10-percentage point increase. Mortality from myocardial infarction has reduced over the last decade; 50% of this decrease is attributed to decreases in incidence and 50% is due to improved case fatality [31]. Therefore, it is possible that the decreased incidence has offset the increases in survival, which would lead to increased prevalence.

There were persistent differences between countries in the overall burden of CVD, with Scotland having a consistently higher burden. Scotland has higher levels of deprivation than the other UK countries, which are a potential explanation for the higher mortality and prevalence levels. The England GBD study showed that different measures of disease burden mirrored deprivation rates [32[. A pooled analysis of 18 cohort studies found that for excess mortality in Scotland, as compared to England, only 25% was explicable by socioeconomic, behavioral, anthropological or biological risk factors [33]; therefore, higher mortality rates in Scotland may also be due to differences in hospital access, ambulance services or case-fatality rates.

The National Service Framework for CHD outlined priorities to be achieved between 2000 and 2010, which included identifying and treating people at high risk, increasing the use of effective medicines for people following a cardiac event, and increasing the number of revascularisations. The increases seen in prescriptions and revascularisation operations in this review indicate that the implementation of this framework was successful [33]. However, it is important to note that these data do not account for increases in population, which are also likely to be a significant contributing factor. This review on trends in the burden of CVD, CHD, and stroke aimed to include the best available data; there are, however, a number of weaknesses. QOF data may be subject to changes in clinical case finding by general practitioners or differences in clinical coding practices [34]. Other sources of prevalence data such as the Clinical Practice Research Database may have similar issues, although this dataset only samples 7% of the UK population.[13] Prevalence reports from surveys face problems of accurately recalling both the type and date of diagnoses [35]. Ideally, we would have reported sex-specific trends in prevalence for all data but QOF data are not available by sex. Finished consultant episodes (both ordinary admissions and day cases) are a proxy for incidence as they do not count people who died before reaching hospital and do not distinguish between people with a first event or a recurring event. We were also unable to provide age-standardised hospital admission rates as these data were not available by age group. Consequently, both hospital admissions and all treatment trends do not take account of the increase in population over time. Prescriptions data include prescriptions that may have been provided as secondary

prevention for people identified as being at high risk for a CVD event; therefore, this should be noted when using the data as a measure of existing burden [36].

Conclusions

From WHO mortality data updated to 2015, IHD remains the leading cause of death in countries of all income groups. However, while IHD mortality is falling globally, mortality rates in many countries, particularly those in lower- and middle-income brackets, remain very high. The prevalence of cardiovascular risk factors continues to rise. Globalization seems to have contributed to a higher prevalence of risk factors in developing countries. Improvement in primary prevention strategies and implementation of public health policies are needed to reduce worldwide mortality from this disease.

Competing interests

The authors declare that they have no competing interests.

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